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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/507,385	09/09/2004	Teizo Yoshimura	4239-64104-02	8908

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EXAMINER	
LEAVITT, MARIA GOMEZ	
ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/507,385	YOSHIMURA, TEIZO	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-33 and 46-57* is/are pending in the application.

4a) Of the above claim(s) *1-10,26-33 and 46-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-25 and 55-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 08-20-2008 has been entered.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
3. **Claims 1-33 and 46-57 are pending**. This application contains claims 11-22, Group III, drawn to a method for inducing maturation of an immature macrophage or an immature dendritic cell comprising contacting the immature macrophage or an immature dendritic cell expressing (Discoidin Domain Receptor 1 (DDR1) with a DDRl-activating agent, elected **with traverse** in the reply filed on 02-05-2007. The following species elected by Applicants in the response filed on 02-05-2007 are also acknowledged: granulocyte-macrophage-colony stimulating factor as the agent that induces the expression of DDR1 (claims 13), a constitutive promoter (claim 16) and a CD-40 ligand as the additional agent that enhances macrophages or dendritic cell maturation (claim 20). Claims 55-57 have been added by Applicants' amendment filed on 08-20-2008. Claims 1-10, 23-33 and 46-54 were previously withdrawn from consideration as being drawn to a nonelected invention, pursuant to 37 CFR 1.142(b), there being no allowable generic or linking claim.

4. Applicants' petition filed under 37 CFR 1.144 is granted, in part. The decision of the petition filed on 10-21-2008 has granted withdraw of restriction requirements between elected Group III and Group IV. Accordingly, Group IV, claims 23-25, has been rejoined with previously examined claims 11-22 and newly added claims 55-57.

5. The requirement is still deemed proper and is therefore made FINAL.

6. Therefore, claims 11-25 and 55-57 are currently under examination to which the following grounds of rejection are applicable.

Response to arguments

Priority

Claims 11-16 and 21-22 find support for the limitation "granulocyte-macrophage-colony stimulating factor" as recited in claim 13 in U.S. Provisional Application No. 60/363,734, 03/12/2002. Claims 17-20 find support for the limitations "DDR1-activating antibody" as recited in claim 17 and the limitation "CD40 ligand" as recited in claim 20 in U.S. Provisional Application No. 60/419,179, 10/16/2002. Newly added claims 55-57 find support for the limitation "the activated intracellular signaling molecules comprise p38 MAP kinase or Shc" as recited in claim 56 in U.S. Provisional Application No. 60/380,978, filed May 15, 2002. Therefore, the effective filing date of 03/12/2002 is used for rejection of claims 11-16 and 21-25, the effective filing date of 05/15/2002 is used for rejection of newly added claims 55-57 and the effective filing date of 10/16/2002 is used for rejection of claims 17-20.

Response to Applicants' arguments as they relate to priority of claims 19 and 20.

At page 9 of Remarks, Applicants argue that claim 19, which depends on claim 11 and not claim 17, does not require a "DDR1-activating antibody", as such claim 19 finds support in U.S.

Provisional Application No. 60/363,734, filed March 12, 2002. The arguments have been found persuasive.

Thus, the Examiner acknowledges that March 12, 2002 is the effective priority date for claim 19.

Additionally, Applicants allege that claim 20 (with regard to the term "CD40" ligand) claims priority from U.S. Provisional Application No. 60/419,179, filed October 16, 2002. "Applicants note that claim 20 is directed to the use of CD40 (among other agents) to enhance monocyte or dendritic cell maturation from immature macrophage or immature dendritic cells. U.S. Provisional Application No. 60/380,978, filed May 15, 2002 clearly discloses that CD40 can be used to induce dendritic cell (DC) maturation (see pages 31 and 58). Thus, if claim 20 is amended in the future to be directed to the use of CD40 to induce maturation of dendritic cells only, Applicants submit that such an amended claim would have an effective priority date of May 15, 2002".

The examiner notes that claim 20 has not been amended to recite the use of CD40, as such October 16, 2002 is the effective priority date for claim 20.

Withdrawn Rejections/Objections in response to Applicant arguments or amendments

Notice of Non-Compliant Amendment- statement under 37 C.F.R 1.4

In view of Applicants pointing out that a statement under CFR 1.497 signed by Dr. Kamohara was submitted with the Supplemental Amendment on September 28, 2007, along with the Declaration under 37 CFR 1.132 and the Declaration For Patent Application, both of which were signed by Dr. Kamohara**, and furthermore,** in view of Applicants' filing of a petition

under 37 CFR 1.48(a) to change the inventorship, the Notice of Non-Compliant Amendment-statement under 37 C.F.R 1.48 has been withdrawn.

Claim Rejections - 35 USC § 102 (a)

In view of Applicant's Declaration under 37 C.F.R. § 1.132 submitted with the September 19, 2007 Amendment as evidence to overcome Kamohara et al., and applicants' allegation "The Declaration state that co-authors T. Yoshimura and H. Kamohara are inventors of the subject matter claimed in the present application. The Declaration also state that the remaining co-authors, S. Yamashiro and C. Galligan, are not inventors of the present application. Thus, Kamohara et al. is a disclosure made by the applicants themselves. As such, it does not satisfy the requirement of § 102(a), which requires an anticipatory disclosure be made "before the invention thereof by the applicant." Furthermore, in view of Applicants' Petition Under 37 CFR 1.48(a) and the Declaration Under 37 C.F.R. § 1.132, evidencing that Kamohara et al. is not available as prior art, rejection of claims 11-16 and 21-22 under 35 U.S.C. 102 (a) as being unpatentable over Kamohara et al., (FASEB J. 2001 Dec;15(14):2724-6. Epub 2001 Oct 15), has been withdrawn

Claim Rejections - 35 USC § 103

In view of Applicant's Declaration under 37 C.F.R. § 1.132 submitted with the September 19, 2007 Amendment as evidence to overcome Kamohara et al. and applicants' allegation, "The Declaration state that co-authors T. Yoshimura and H. Kamohara are inventors of the subject matter claimed in the present application. The Declaration also state that the remaining co-authors, S. Yamashiro and C. Galligan, are not inventors of the present application.

Thus, Kamohara et al. is a disclosure made by the applicants themselves. As such, it does not satisfy the requirement of § 102(a), which requires an anticipatory disclosure be made "before the invention thereof by the applicant." Furthermore, in view of Applicants' Petition Under 37 CFR 1.48(a) and the Declaration Under 37 C.F.R. § 1.132, evidencing that Kamohara et al. is not available as prior art, rejection of claims 11-19 and 20 under 35 U.S.C. 103(a) as being unpatentable over Kamohara et al., (FASEB J. 2001 October 15, pp. 2724-6. Epub), in view of Lipford et al., (US Pub No. 2003/0148316, Date of Publication August 7, 2003), has been withdrawn

New grounds of rejection

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 12 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language.

Claim 12 depending on claim 11 recites "further comprising contacting the immature macrophage or the immature dendritic cell that expresses DDR1, or a precursor thereof, with an agent that induces the expression of DDR1". The cell recited in claim 12 appears to already express DDR1. Thus it is unclear the functional role of the agent that induces expression of DDR1 in cells that already express DDR1. As such, the metes and bounds of the claims cannot be determined.

Claim 14 which depends on claim 13 recites "wherein contacting the immature dendritic cell or the immature macrophage with an agent that induces expression of DDR1 comprises transfecting a monocyte or a dendritic cell precursor with a nucleic acid encoding DDR1b operably linked to a promoter". It is unclear how transfection of immature dendritic cell or the immature macrophage with a nucleic acid encoding DDR1b brings about the claimed contacting of the immature dendritic cell or the immature macrophage with the agent that induces expression of DDR1, as recited in claim preamble. As such, the metes and bounds of the claims cannot be determined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 11-25, 55, and 57 rejected under 35 U.S.C. 103(a) as being unpatentable over Radziejewski et al., (US Patent 6,022,694, Date of Patent Feb 8, 2000), in view of Lipford et al., (US Pub No. 2003/0148316, Date of Publication August 7, 2003).

Radziejewski discloses methods for promoting the growth, proliferation, differentiation, and/or survival of cells that express in their surfaces a receptor-like tyrosine kinase as Discoidin Domain Receptor (DDR1) comprising contacting the cell that expresses the DDR1 receptor with a DDR-1-activating agent (col. 12, lines 66-67, bridging to col. 13; col. 15, lines 24-31; col. 24,

lines 15-17). Note that COS cells used to express the DDR1 receptor were cultured in 10% BCS/DMEM. Thus any of the protein components in the serum is inherently a DDR1- activating agent **(Current claim 11).** In addition, Radziejewski discloses that subsequently, after serum removal from the medium, cells expressing DDR1, were further contacted with collagen to induce expression of DDR1(col. 15, lines 33-35) **(Current claims 12 and 19).** Moreover, binding agents to DDR1 include antibodies specific for in vitro screening of cell lines that expressed DDR1 including rhabdomyosarcoma, glioblastoma, sarcoma and epithelioid carcinoma cell lines (col. 10, lines 48-50; col. 16, lines 1-10) (**Current claims 17 and 22**). In addition, Radziejewski discloses genetically engineered cells able to express DDR1 by transfecting cells with a vector encoding a gene expressing DDR-1 under the control of a CMV promoter and other promoters (col. 9, lines 18-21; lines 25-30, lines 40-46) (**Current claims 14, 15 and 16**). Furthermore, Radziejewski describes in vitro assays wherein cells expressing DDR1 are contacted with collagen and a test agent including peptides and non-peptide agents to test for collagen activity (col 8, lines 18-53; col. 9, lines 1-5; col. 11, lines 6-12)**(Current claims 23 and 24**) In addition, Radziejewski teaches that receptor tyrosine kinases recognize and respond to peptide growth factors such as insulin, platelet-derived growth factor and nerve growth factor (col. 1, lines 22-25) and ligand binding to DDR1 receptor ectodomain leads to activation of downstream signaling molecules (col. 1, lines 35-40) **(Current claim 55)** .

Radziejewski does not specifically disclose differentiation of dendritic cell expressing DDR1.

However, at the time the invention was made, Lipford et al., teaches the process of maturation of dendritic cells from PBMC by treatment with GM-CSF and IL-4(p.1, [004] [005])

(Current claim 13). Moreover, Lipford et al., discloses on page 7, Table 1a, a list of cell surface markers expressed in resting or unstimulated state of myeloid-like DCs precursor DC type 1 (i.e., plasmacytoid dendritic cells, **pDC1**) including DDR1 (Table1a, rank 165, Accession #U48705) and cell surface markers including DDR1 that are induced or upregulated during immunostimulation (p. 18, Table 5c, Rank 17, Accession # U48705; p.2, [0015]). Furthermore, Lipford et al., teaches that maturation of dendritic cells to professional APCs can be initiated by T cells expressing CD40 ligand (CD40L)(col. 1, [0004]) **(Current claim 20).** Lipford et al., teaches agents that stimulate pDC including anti-CD40 antibodies (p. 20, [0110]) and discloses the use of such agents in the stimulation and/or attenuation of dendritic cells either *in vivo* or *ex vivo* (p. 27, [0172]) **(Current claims 21 and 22).** Lipford et al., teaches that monocyte-derived DCs (MDDCs) are activated by antigens including endotoxins, dsRNA, immunostimulatory bacterial CpG-DNA and others (p. 1, parag. [0008])**(Current claims 24 and 25).** In addition, Lipford et al., teaches that Mature DCs release soluble mediators, such as cytokines and chemokines (p. 1, parag. [0004])**(Current claim 57).**

Therefore, in view of the benefits of contacting a DDR1 expressing cell with a DDR1-activating agent to induce differentiation of said cell as taught by Radziejewski, it would have been *prima facie* obvious for the skilled artisan to have contacted any of the cells expressing DDR1, including dendritic cells, with the DDR-1 activating agent in order to induce cell differentiation and/or proliferation. Moreover, it would have been *prima facie* obvious to further contact dendritic cells with GM-CSF in addition to a DDR1- activating agent, to obtain a population of mature dendritic cells with a reasonable expectation of success, particularly since Lipford et al., teaches maturation of dendritic cells from PBMC by treatment with GM-CSF.

Alternatively, it would have been *prima facie* obvious to additionally contact dendritic cells with a CD40 ligand in addition to a DDR-1 activating agent, particularly because Lipford et al., teaches that maturation of dendritic cells to professional APCs can be initiated by T cells expressing CD40 ligand. Further, based on the detailed teachings of the Radziejewski patent, the Lipford publication and the high level of skill in the art of molecular immunology, the skilled artisan would have had a reasonable expectation of success in contacting dendritic cells with a CD40 ligand or GM-CSF in addition to a DDR1- activating agent to induce dendritic cell differentiation, as Lipford et al., discloses the presence of DDR1 in dendritic cells and Radziejewski actually evidences growth, proliferation, differentiation and/or survival of cells expressing DDR1 by contacting said cells with a DDR1-activating agent.

Claim 56 is rejected under 35 U.S.C. 103(a) as being unpatentable over Radziejewski et al., (US Patent 6,022,694, Date of Patent Feb 8, 2000), in view of Lipford et al., (US Pub No. 2003/0148316, Date of Publication August 7, 2003) a applied to claims 11-25, 55, and 57 above, and further in view of Vogel et al., (WO 98/34954; Date of Patent 13 August 1998).

The teachings of Radziejewski et al., and Lipford et al. are outlined in the paragraphs above. In addition, Lipford discloses up modulated genes (e.g., downstream signaling molecules) in human pDC including MAP3K8, mitogen-activated protein kinase kinase kinase 8 ; MAP3K14 (mitogen-activated ptoein kinase kinase 14) (page 11, Table 2a, rank 70; page 15, Tabel 2c, Rank 86). The combined disclosure failed to teach activation of the Shc intracellular signaling pathway.

However, at the time the invention was made, Vogel et al., discloses that collagen activation of DDR1 induces phosphorylation of a docking site for the Shc (page 2, lines 1-6).

Therefore, in view of the benefits of contacting a DDR1 expressing cell with a DDR1-activating agent to induce differentiation of said cell as taught by Radziejewski, it would have been *prima facie* obvious for the skilled artisan to have contacted any of the cells expressing DDR1, including dendritic cells, with the DDR-1 activating agent in order to induce cell differentiation and/or proliferation. Moreover, it would have been *prima facie* obvious that the contacting with a DDR1- activating agent would had activated any of the downstream signaling pathways mediated by DDR1 including Shc as taught by Vogel et al., Thus based on the detailed teachings of the Radziejewski and Vogel patents, the Lipford publication and the high level of skill in the art of molecular immunology, the skilled artisan would have had a reasonable expectation of success in contacting dendritic cells with a DDR1- activating agent to induce dendritic cell differentiation and activation of Shc signaling molecule, as Lipford et al., discloses the presence of DDR1 in dendritic cells, Radziejewski actually evidences growth, proliferation, differentiation and/or survival of cells expressing DDR1 by contacting said cells with a DDR1-activating agent, and Vogel et al., teaches that collagen activation of DDR1 induces phosphorylation of a docking site for the Shc molecule .

Conclusion

Claims 11-25 and 55-57 are rejected

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding his application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Maria Leavitt/

Maria Leavitt, PhD
Examiner, Art Unit 1633